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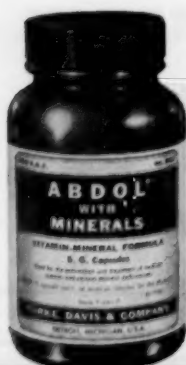
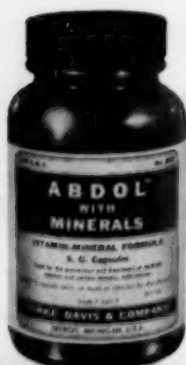
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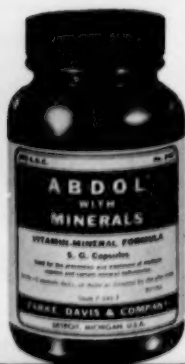
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E D I T O R I A L

IT CONCERNS US ALL

IN the current efforts to remove all restrictions pertaining to the place of sale of drug products labeled "with adequate directions for use", the feeling seems to be prevalent that this is a matter of concern for retail pharmacists only. Nothing could be further from the truth.

The present situation in the drug field is such that every subdivision of it has been doing pretty well and our record of service to the American people, as well as our return for our services, deserves neither criticism by others nor complaint by ourselves. In spite of all minor irritations—and even a few major problems—things are going along well, for which we can be happy. Let us, however, inquire what would be the effect on pharmacy in its broadest sense if the retail pattern of distribution of over-the-counter drugs were greatly altered so that pharmacy were no longer the chief area or outlet for their sale. The immediate impact, of course, would be on the retail pharmacist himself. In fact, a large majority of pharmacies are able to render a prescription service and other professional services to their community only because certain ancillary activities provide a broad base of operation keeping the enterprise solvent.

Should the retail drugstore cease to be the principal outlet for over-the-counter remedies, the number of pharmacies would of necessity be drastically curtailed. On the surface, this might not appear to be of any serious consequence, but what about the economic health of the various businesses in the United States whose customers are retail pharmacies? Is the closing of hundreds of drugstores of no concern to the members of the National Wholesale Druggists' Association and the Federal Wholesale Druggist's Association? We feel sure that it is. What about the impact on the manufacturer of purely "ethical" prescription products? As every economist knows, the sale of a product is influenced greatly by the number of outlets through which it can be obtained. Would these manufacturers, indeed, like to do most of their business with hospitals, realizing that many hospitals buy largely on a price basis? And do they expect that detailing could be successfully done if the product could be obtained only in a few widely scattered pharmacies? Would not the distributive pat-

tern of today's prescription specialties be grossly altered and would the change be favorable to the best interests of the drug industry?

In retail pharmacy's fight with certain proprietary interests, the American Drug Manufacturers' Association and the American Pharmaceutical Manufacturers' Association have chosen to sit in the sidelines. In some cases, their member companies may have little choice since top management operates both an "ethical" pharmaceutical house as well as a company devoted to the manufacture and distribution of over-the-counter products. In such cases, of course, it would be difficult to take sides but should this prevent companies that are not so divided in their interests from helping the beleaguered pharmacist fight his battle for survival?

Were it solely a matter of economic interest, it would not be so ironic that pharmacists have so little support, but is there any clear thinking person who feels that drugs of any sort can be purchased and used by the average layman with complete safety, using only the data presented on the label? If, in our present organization of society, a man cannot cut hair or fix someone's plumbing without a license certifying training qualifying him to do so, is it not reasonable to expect one who sells drugs to be similarly trained and licensed—or are one's bathroom fixtures of greater importance than one's own body?

Even those interests who now are trying to broaden the retail distribution of drugs have no real cause for complaint in the distribution given their products by retail pharmacy. It has been largely retail pharmacy which has built up their sales to the phenomenal level which they now enjoy. Is there no limit to industry's desire for increased sales and are no considerations of greater importance than this?

In summary, it would be well for all segments of pharmacy to think carefully on the trend which things are taking and the likely end result. This is a matter of concern for all and not one which affects only a few.

L. F. TICE



THE PUBLIC RELATIONS VALUE OF A COLLEGE OF PHARMACY DIPLOMA AND A STATE BOARD CERTIFICATE (PART I) *

By Robert L. Swain

AS it was I who suggested this title, it was more or less logical, I presume, to ask me to discuss it. But, aside from the logic of those who prepared the program for this meeting, I am very happy to explore the subject, because I think it has within it those facts and implications which can be made to play a vital part in improving pharmacy's standing with the public and bringing the public to a much sounder conclusion with respect to the basic significance of pharmacy and the drug store to community health.

As this subject has for its objective the betterment of pharmacy's relations with the public, it would seem desirable to establish some basic facts regarding pharmacy and the retail drug store, as it will be from an understanding of these facts than an effective approach to the public will most likely come.

Some wag once observed that the corner drug store is as typically American as Plymouth Rock or apple pie. And, while in a sense this may be looked upon as complimentary, the possibility of having the drug store seem as something typically run-of-the-mine, and therefore not distinguishable from other typical outlets or establishments, is distinctly a disadvantage.

As a matter of fact, do we want the drug store to be a typical, routine species of retail outlet, or do we want it to stand out as reflective of pharmacy as a health care profession? Do we want the drug store to be classed with that which is typical of stores in general, or should we seek to have it known by the public as the safe, logical, and dependable place at which to purchase such vital every-day necessities as drugs, medicines, sick room supplies, first aid material, and the many other products and commodities which play so large a part in the treatment of disease and the conservation of health?

Let's consider some fundamental facts regarding the pharmacy and the retail drug store. First of all, extremely basic is the fact that the pharmacy or drug store is a store and that it partakes of many of the characteristics of stores as a class.

* Presented at the Meeting of the Boards of Pharmacy and Colleges of Pharmacy of District No. 2. Hotel Shoreham—Washington, D. C., October 31, 1955.

The drug store is located on the street, with the supermarket, hardware store, delicatessen, novelty shop, shoe store, Five and Ten, and all kinds of retail outlets. The drug store buys and sells merchandise. It has window and interior displays. It has shelving, tables, islands, counters, show cases, wrapping counters, and cash registers. It goes in for a wide range of merchandising, the majority of which has little or no health significance, and no valid relationship to pharmacy and pharmaceutical service. It maintains an automobile for delivery service, and engages in many activities which go hand in hand with mercantile operations.

It is against this mercantile and distributional background that pharmacy must in some way maintain its professional status and integrity. It is in the light of this merchandising intensity that we must seek to make the public vitally aware that the drug store is the site of an essential professional health service, and that it is truly a neighborhood health service institution.

Some difficulties in the way of having pharmacy assume its proper professional stature in what is essentially a commercial institution, so far as public appreciation is concerned, can be emphasized in a few pertinent observations. First of all, pharmacy is the only profession practiced in a commercial environment and as this commercial environment partakes of the intensity born of violent competition, it is seen as a force against which pharmacy, as a profession, must fight for its place in the sun.

There is, and inevitably must be, a conflict between the profession of pharmacy and the business of the drug store. Competitive pressures give rise to still more pressures, with the result that the drug store becomes so engulfed in its feverish rush for competitive security that, in appearance at least, it tends to coalesce into the more or less turbulent competitive scene.

The conditions under which the drug store operates are bound to emphasize its merchandising character and to tend to minimize its professional service. In a very real and practical sense, the cards are stacked in favor of the merchandising and competitive aspects of the drug store and against its professional health services. We need fully to recognize these facts, because they must be offset and controverted to a high degree if pharmacy is to enjoy any semblance of recognition and support as a professional health calling.

One reason, perhaps, why pharmacy as a profession remains under heavy pressure is because pharmacists as a body have not been

alert to the true meaning of these facts, or else have been too little concerned with their fateful consequences.

The fact that we know pharmacy is a profession, and that the rendering of a pharmaceutical service is truly a professional function, is all the more reason why we should resolve to bring about those fundamental changes in our attitudes so essential to giving pharmacy its proper place in public estimation and esteem.

As I have said many, many times in writings and addresses before pharmaceutical bodies, we must merchandise our basic resources back to ourselves, at the first step in making them appeal to others. We must come to the proper evaluation of these resources before we can possibly hope to give them high standing in the public mind.

It is axiomatic that the public will accord pharmacy the same value that we ourselves give it, but that it will not outbid us in an effort to give pharmacy a higher public standing than we give it in our own drug stores.

Now, let's emphasize some matters inherent in pharmacy and the drug store which would seem to possess an immense public relations value. Prescription practice is running over one billion dollars annually, and represents, throughout the country as a whole, twenty-five per cent of drug store volume. When we add to this total the volume in prescription accessories and other professional items and services, we reach the conservative conclusion that at least forty per cent of our day by day activities warrant being classified as professional in character.

We fill about five hundred million prescriptions a year, which means that for five hundred million times a year, the sick and ailing come to us for a professional health service which only we can provide. Therefore, pharmacy looms forth as a calling utterly indispensable to the health and well being of our people.

The tragic fact is that while pharmacy is indispensable in its contributions to public health, it is not permitted to reflect this character in thousands of retail drug stores throughout the country. In spite of the indispensability of its health care services, we find pharmacy crushed under the weight of merchandising activities, the inevitable effect of which is to squeeze pharmacy into a minor or inferior position.

Even though our prescription service is packed so full of the drama of human life, there are many drug stores—far too many—in which merchandising is carried on with that abandon which makes

the prescription department, when discernible at all, seem sharply out of place.

We have much on which to build but the pity is we have not done so with any marked degree of efficiency. Pharmacy has been left to shift for itself, with many of us making its task much more difficult than it need be.

While it is true that pharmacy is the one profession practiced in a commercial environment, it is also true that the drug store is the only store which, through the force of law, must be conducted by a college or university graduate. This is a basic and fundamental fact.

We have known this all our lives, but does the public know it? Does the public see us in terms of our college training?

Has the public recognized this training in its differentiation of the pharmacy from all other stores?

Have we made any worthwhile effort to drive home the concept that the pharmacist is the only retail operator required by law to be a college or university graduate?

That these questions can be asked at this late day is sufficient answer to them. We have not made much effort, if indeed we have made any, to acquaint the public with the truly distinguishing facts about the drug store and the pharmacist.

By the way of emphasis, let it again be said that the drug store is the only store which must be conducted by a college or university graduate, and the pharmacist is the only retail dealer the law requires to hold a diploma from a college or university.

But this is not all. The retail drug store is the only store in which will be found displayed the Certificate of Registration which is issued by the State itself, and which the State demands must be prominently displayed in the drug store.

This Certificate, it should be pointed out, cannot be bought, it cannot be borrowed, it cannot be stolen,—it must be earned. How is it earned? By mastering the curriculum embraced within four years of college or university training, and by having successfully passed an examination which the State conducts in its own name.

The Certificate is really a statement to the public, by the State itself, that the person whose name appears on it is a competent pharmacist, and qualified to meet the needs of the public for a professional pharmaceutical service.

Here, again, we know the facts, but does the public know them? By and large, has the public the slightest appreciation of what the

State Certificate means and implies? Do they see it in terms of its professional import? In many retail drug stores, do they see it at all?

Now we can ask, what public relations value is inherent in the college of pharmacy diploma and the Certificate of Registration? In what sense can they be made to contribute to raising pharmacy and the drug store in public estimation and esteem? In what manner can they emphasize the basic health functions of pharmacy and the drug store?

These questions, so it seems to me, are answered by the fact that the diploma and the Certificate are exclusively ours. No one but a pharmacist can possess or display a college of pharmacy diploma. No one but a pharmacist can possess or display a State Board Certificate.

Again, these are exclusively ours, and, as I see it, they constitute basic resources of pharmacy which can be made to exert a tremendous impact upon public opinion. And, once this impact is exerted, it would seem logical to assume that the drug store would instinctively acquire a stronger position in the appreciation and evaluation of the public.

I have no doubt that the Certificate and the diploma can be made to stand out as symbols which identify the drug store. Indeed, perhaps the time has come when we should regard them as the veritable trade-mark of pharmacy and so focus their meaning upon the public as to strengthen the drug store in all economic and professional respects.

If these are ours and ours alone, common sense suggests that we use them to promote our best interests. If these are ours, and exclusively ours, why should we not use them to serve in the most effective way to express and expand the professional integrity of pharmaceutical service?

If these are ours, and ours alone, why should we not make them stand out in our drug stores as the basic characteristic of everything we want pharmacy to mean in public estimation and esteem?

I should like to see the college of pharmacy diploma and the State Board Certificate prominently displayed in every retail drug store and constructive effort made by our pharmaceutical organizations to educate the public with respect to what they mean.

Now, this might require our colleges of pharmacy to have their diplomas suitable for the purposes emphasized here, and also to call upon the Boards of Pharmacy to issue Certificates of Registration suitable for this purpose. I don't have in mind diplomas and cer-

tificates of heroic proportions, but I do have in mind diplomas and certificates of such size and dignity that we could proudly use them as symbols of our profession and as the veritable trade-mark of our professional services.

The matter of pharmacy's public relations is becoming of greater significance day by day. The conviction is being accepted that many of the problems now confronting our profession depend largely upon public attitudes toward pharmacy for their solution. This is brought into sharp outline by the changing pattern of distribution now so evident in all divisions of retail trade. As the pattern changes, competition becomes more intense, with the result that the retail drug store is bound to be drastically influenced by the competitive forces which abound in all fields.

There is now going on, as we all know, a drift of drug store products into non-drug outlets, and by many observers of the current economic outlook for the drug industry, this is regarded as one of the really fundamental phases of the changing pattern of distribution. Undoubtedly these changes constitute a threat to the economic and professional stability of the retail drug store, and pharmacy necessarily has a vital stake in the attitudes of the public to the changes taking place.

All of which means that pharmacy is faced with the urgent need to drive home to the public the basic concept that the drug store is the safe, logical, and dependable source of drugs and medicines, and the many other products used in medical care.

Pharmacy is faced with the urgent need, also, to make the public see the drug store in terms of personal and individual health care needs. It needs to see the drug store in the light of individual safety. These needs could, in my judgment, be largely served by impressing upon the public the meaning of the college diploma and the Certificate of Registration. Certainly an appreciation of what these mean might lead the public to differentiate the drug store from other retail outlets, and to distinguish the pharmacist's functions from other retail distributors.

It seems to me that it would inevitably lead to a higher appreciation of the intrinsic value of pharmaceutical service. Would we not gain if the public could be led to look for the diploma and certificate in every place in which they sought to buy drugs, medicines, and other related health products?

Would we not gain if the public could be led to forego the purchase of these essential health needs in any place other than a pharmacy in which the diploma and certificate are displayed? Would we not gain if the public could be educated to see the diploma and certificate as symbols of a safe, logical, and dependable drug store service, and as the trade-mark of a calling indispensable to the health and well being of every man, woman, and child in America? Would we not gain by so interpreting the diploma and the certificate to the public that they would come to associate them with its own welfare and self-interest?

Now, in discussing the diploma and Certificate of Registration as among our basic pharmaceutical resources, we should become all the more conscious of the need to study all our resources and they are many, so that they may be presented to the public in their true and proper sense.

It would stand to reason that if we as pharmacists had a complete grasp of the full significance of pharmaceutical resources, we would instinctively modify or re-shape our conduct and our drug stores so as to properly impress them upon the public.

We hear a great deal about the need to make the public pharmacy-conscious, but to me this is merely an empty phrase until we ourselves become intelligently pharmacy-conscious. It would seem a basic proposition that we must first merchandise our resources to ourselves before we may possibly hope to have them well and favorably received by the public.

Now, as a final observation, it would seem reasonable to assume that if we should attempt to build a public relations program around the full meaning of the college diploma, and the State Board Certificate, together with a powerful interpretation of the significance of our resources, to the public welfare, they might have that impact upon pharmacy which would make the drug store much more reflective of the meaning of our basic resources.

The mere reflection on this subject conjures up a consummation devoutly to be wished. Let us keep in mind that pharmacy's standing with the public has become vitally important to the survival of the drug store as a drug store, and the permanency of pharmacy as a public health profession, and the sooner we become dedicated to a fundamentally sound approach to this matter, the greater will be our contribution to the future usefulness of our profession.

THE PUBLIC RELATIONS VALUE OF A COLLEGE OF PHARMACY DIPLOMA AND A STATE BOARD CERTIFICATE (PART II) *

By William L. Blockstein **

DR. SWAIN has done much more than he said he was going to do in his introductory paragraph. He said that he was going to explore the topic. Rather than exploring, he has surveyed the area, marked its boundaries, and defined the scope of the discussion. Since Dr. Swain's remarks need no further amplification, I should like to offer some points illustrating how I feel that the public relations value of a college of pharmacy diploma and a state board certificate can be enhanced.

If, as Dr. Swain indicates, forty per cent of our day-to-day activities are professional in character, should we redesign our pharmacies to allow selling and display space on an equivalent basis—sixty per cent for sundries and other types of merchandising, forty per cent for prescriptions and related professional services? Or can we, within the present framework of our pharmacies make our prescription departments and our professional services so outstanding that they tell the story of pharmacy's resources without the need of a 60-40 breakdown?

That this is being done and can be done was indicated by a speaker at the Pennsylvania Pharmaceutical Association's convention this summer. He stated that of all new store construction and remodeling work in retail pharmacies, an increasing percentage of the jobs were designed and built with the prescription department right up front, with a plate glass window facing the street. In this type of installation, the public sees pharmacy and its professional services constantly.

With pharmacy on view before the public, pharmacy can expect the public to have a greater appreciation for it and its place in the

* Presented at Meeting of the Boards of Pharmacy and Colleges of Pharmacy of District No. 2. Hotel Shoreham, Washington, D.C. October 31, 1955.

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health professions. Remember, the public doesn't appreciate what it doesn't see or understand. What happens when the average pharmacist receives the average prescription? He disappears, returns a while later, and states a price. The patron doesn't know what took place, and can't know as long as the pharmacist works in a secret or semi-secret place. The pharmacist has one of two choices: he can invite his patrons into his prescription department to watch him at his professional work, or he can take his prescription department out front and put it on public view.

A part of public relations is public understanding. Understanding is compounded of a variety of things—sympathy, respect, and appreciation, among others. Understanding is not, and has never been, composed of lack of knowledge. And, aren't you keeping knowledge from your patrons when you disappear into the back of your pharmacy to fill your prescriptions? The physician, when he uses his stethoscope, doesn't go into another room to listen. He is right where the patient can see him. The patient may not know exactly what is going on, but at least he can see some of the procedure. I submit that the same can be applied to pharmaceutical practices. Move your prescription department out front; let the patron watch you at work. He may not understand everything you do, but he'll have a greater appreciation and respect for your professional activities. I might add that, if you do move your prescription department out front, you will have a much better display space for those two certificates that serve to set you apart from the rest of the men on the street. These certificates can be displayed very prominently on the wall, or on the glass partition of your prescription department, where they should be tastefully framed, well lighted, constantly dusted, and cared for. They will serve as constant reminders to the public of who that white-coated man is and just what it is that makes him different from others.

While on the subject of white coats, I am reminded of the story told me by a former board member from a nearby state. He said that since the rise of the television commercial, white coats were as common as black Model T Fords used to be. For a while he was tempted to give up his white coat. He thought better of it, however, and decided to add a touch that would set him apart from most other white-coat wearers. He moved his prescription department up front, enclosed it in glass, and put his sink right where every patron could

see it. Every time that he stepped into his prescription department, he washed his hands. Just a simple thing—handwashing—but it was enough to emphasize the importance that he himself placed on his professional activities, and served as an indication of the respect that he himself felt for pharmacy.

It is not enough for a pharmacist alone to place pharmacy in the best possible light. It is the responsibility of his apprentices, and his other employees to serve as symbols of professional standards.

All employees learn their habits and attitudes from their employers. All of your employees can do much to determine whether you have good or bad public relations. As Burt Mull recently observed, "We all have public relations, the only question is whether they will be good or bad." I submit that your employees are not as bound by ties of loyalty as you may suppose, and if your professional or business habits are not all they should be, the community will learn of this fact. Your employees are people; they have friends and associates outside the walls of your pharmacy, and they talk. If you want them to speak well of you at all times, you must conduct yourself as Caesar's wife—above suspicion. A good employer can use his employees as his public relations agents by developing good habits and attitudes in them; by acquainting them with the resources of the profession of pharmacy; by pointing out pharmacy's service nature; and by continually relating pharmacy to its sister professions on the health care team.

I have purposely considered apprentices to be a special class of employees, for they will be the pharmacists of the future. Theirs is a double opportunity for public relations—as apprentices now, and as pharmacists later.

This job of selecting and training the pharmacists of the future is a joint responsibility of the practitioner and of the schools of pharmacy.

The requirements for apprenticeship training state that an apprentice shall perform his functions under the direct supervision of a registered pharmacist. The state does not restrict certain apprentices to certain pharmacists, for registration grants an obligation to all pharmacists to serve as preceptors. The state does not say that this or that type of pharmacy is the place where an apprentice can learn best. The state merely says that a registered pharmacist must supervise apprentice training.

Pharmacists do themselves and their profession a disservice when they refuse to hire apprentices. And make no mistake, there are pharmacists who will not be "bothered" with taking an apprentice into their employ and instructing him in the art and science of the profession. As long as the state recognizes a registered pharmacist as a preceptor for professional training, the pharmacist must live up to his responsibilities by training apprentices.

Training apprentices means more than just hiring a young boy or girl and permitting that person to hang his or her shingle on the wall. It imposes definite responsibilities on the preceptor to train and educate his apprentice in every way that he can to be a good professional man, as well as give him some insight into the business end of pharmacy. An apprentice is not a source of cheap labor, bound to serve out his hours in order to qualify for an examination. An apprentice is a young person who is eager to learn as much as he can about the profession he has chosen as his calling in life. He ought not be exploited; nor should he be coddled. He should, however, be given the opportunity to perform varied duties, always under careful supervision, so that his period of apprenticeship will serve as a distinct adjunct to his formal education in a school of pharmacy.

Now, let's talk specifically about those twin certificates which symbolize much of what I have said about the general resources of the profession. There are a number of other ways to enhance the public relations value of these certificates, three of which I want to discuss here:

- Promoting your college diploma in all of your activities,
- Calling attention to your state board certificate, and
- Recruiting good candidates for the profession.

In the first place, a college of pharmacy diploma does not serve as a public notice of divorcement between college and alumnus. For the rest of his life, a pharmacy graduate is bound up with the successes and failures of his alma mater. As his school increases in prestige, so do his diploma and his stature as a college graduate increase in value.

If the pharmacy graduate's future is tied up with that of his alma mater, how can he make sure that the future stays bright? He should act as though he is proud of his alma mater; he should be

enthusiastic toward its aims and purposes; and he should support it in every way at his command.

I don't mean that he should walk around with a sign on his back saying, "I'm a graduate of so-and-so U." I do mean that he should take an interest in *everything* his alma mater does, from the football season right on through research projects to commencement time, and then start all over again. Alumni giving is fine, and should be a part of every alumnus' program, but it isn't the end of this prestige building program. It takes its place along with visits to the campus, with speaking about the old school, with interesting young people in studying there, and with all of the many ways that you yourself can think of to promote the prestige of your school. It's only good business to identify yourself with a good thing. I have a friend who is in a very high place in educational circles. He tells me that he is a graduate of the Agricultural College of Massachusetts. Naturally, he is quite proud of his diploma and what it stands for. After his graduation, the school changed its name, because of a diversification of interests, expanded educational program, and community and alumni interest. He tells me that his diploma increased in value overnight when he became a graduate of the University of Massachusetts. Yours can do the same, even without a name change, if you work at it from two ends—your alma mater's as well as your own.

Working at this from your end takes many forms. Your prescription labels, your business letterheads, your store identification, as a matter of fact, all your professional identification should carry your degree, as well as the initials, R. P., which signify the state's approval of your right to practice pharmacy. At this point, I suppose I am at odds with our friends from New Jersey. My personal feelings are that the initials, R. P., alone do not mean enough to the public. And, for that matter, neither does Ph. G. or B. S. mean enough. As Dr. Swain points out, a pharmacist is both a college graduate and a state-licensed man. The public should be told this at every opportunity.

Just as your diploma is as good as you and your school make it, so your certificate is as good as you, your colleagues, and your board members make it.

Dr. Swain has told you how you and your colleagues can call attention to your professional activities, and how to make your prescription department the real center of your pharmacy. I think that you need to be reminded that board members have a stake in this

question of public relations. Board members represent authority in pharmacy to the public; therefore, board members should be truly representative of professional pharmacy and its resources. Not every pharmacist can serve on a state board, but every pharmacist should have a say as to who does serve. In most of our states, board members are chosen not only for pharmaceutical background, but also for political affiliation. As long as this situation exists, pharmacists owe it to themselves to be politically active. In this manner, no matter what turn politics may take, organized pharmacy can recommend the best qualified candidates for board membership.

Not only must pharmacy work at placing itself on public view to enhance public understanding in the immediate sense, but it must also embark on a long-range program of attracting highly qualified candidates to the profession for its future.

Selection of recruits for a profession is one of the proudest privileges granted to members of a particular profession. It is a privilege that should not be held lightly nor treated carelessly. Any profession that is constantly in need of professionally trained personnel may find itself recruiting under unusual circumstances. In our recruiting for pharmacy, through our own enthusiasm, we may lay more emphasis on what the field offers the worker than on what the worker can offer the field. In our desire to provide replacements, we may induce and encourage recruits for pharmacy who lack the qualities needed in a good pharmacist.

Many pharmacy students fail to graduate from schools of pharmacy, and the greatest mortality appears to be in the beginning year. Aside from financial reasons, illness, family problems, and so on, there is another reason for dropping out: that of misdirection—misdirection by a well-meaning pharmacist who mistook agreement for enthusiasm, silence for steadfastness of purpose, and interest for burning desire.

Recruitment could be more than just getting young men and women to enter a school of pharmacy. It could be not only a screening process carried on by every pharmacist for recruiting's sake alone, but also for the public relations value of educating people about pharmacy. It is telling our young people about pharmacy, showing them what pharmacy is and what it is not, and possibly motivating them toward pharmacy, and stimulating their interest in it.

No matter what course recruiting takes, it should be a more effective recruitment, at the same time that it is a more selective recruitment. This will assure the long-range public relations value of both

of our prized certificates of honor and trust. We will have gained recruits for our profession, and gained an appreciation and recognition for pharmacy in all to whom our story has been told.

In summary, then, these are some of the points that illustrate how the public relations value of a college of pharmacy diploma and a state board certificate can be enhanced:

- Make your prescription department stand out above your many activities by relocating it in the front of your pharmacy;

- Use all your employees and especially your apprentices as public relations agents for professional pharmacy;

- Train your apprentices so that they can carry on professional and public relations activities for pharmacy;

- Promote your diploma and your certificate by supporting your alma mater and your state board; and

- Recruit good candidates for pharmacy with two aims in mind: one—recruitment alone; and, two—winning friends for pharmacy by educating the non-recruits about pharmacy.

AN INTRODUCTION TO THE HISTORY OF MEDICINAL CHEMISTRY

By George B. Ceresia * and Charles A. Brusch **

ALTHOUGH the beginning of Medicinal Chemistry was associated with the sorcerer, soothsayer, charlatan, healer, medicine-man and general quack, men, who for the most part sought money and power by investing themselves with supernatural powers, we must credit them with the perpetuation of medicinal knowledge in times when there were no printing presses and a scarcity of writing materials. Placation of the gods by burning certain herbs; sale of love potions to ardent suitors, use of amulets and small sacks containing aromatics as defense against evil spirits and advertisement of nostrums or elixirs as cure for any physical disabilities, all, contributed humbly to the development of medicinal science.

There are accounts in the Bible which mention "oil of myrrh" and "oil of Balsam", names which themselves have a healing sound. References to vinegar, nitre, fuller's sope and even Noah's experiences in the preparation of intoxicating beverages in the scriptures show that such things were known in those times. Knowledge of refining sugar, fermentation of wine, extraction of vegetable oils, rendition of animal fats and saponification procedures were known early in the history of man.

The remedial agents employed in ancient Babylonian-Assyrian culture were varied in nature and comprised a list of 250 vegetable drugs as well as a smaller number of drugs of mineral and animal origin. Prescriptions include mixtures of honey, syrup of dates, herbs of different kinds, rubbing oils, medicated clysters and rubbing salves. There were, also, secret remedies bearing such mysterious names as "the Sun God's remedy", "the dog's tongue", "the skin of the yellow snake", etc., which presumably were more psychologically than physiologically therapeutic.

The Egyptians, closely allied to the Babylonian-Assyrian culture, wrote their prescriptions and remedies in papyri. As was the common

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practice of the times, excrements of men and beasts as well as products of bacterial decomposition are found in the *Materia Medica*. The urine of man was differentiated according to sex and age, for the purpose of potency and specific application. Directions for the oral administration of decoctions, infusions, injections, pills, tablets, troches, capsules, powders and inhalations were given along with instructions for compounding and methods of disguising bad-tasting medicinals. Directions were given, also, stating whether the prescription was to be taken internally or externally, whether it was to be taken frequently or over long intervals of time and at what particular time of day or night, for the optimum effect. Here each physician was a specialist and dealt with but one disease.

The vegetable drugs of ancient Egypt were used fresh or dried in the sun. Mortars, sieves and hand mills were used in the production of powders. As a result, Egyptian medicine reached its full development before 1600 B. C. But from then on degenerated and largely assumed the form of sorcery and medicine-manism.

The medicinal chemistry of Greece and Rome is very similar, mostly because the Romans borrowed from the Greeks. The Greeks in contrast to oriental peoples, were strongly individualistic and thus there was a transition from the priest-medicineman to the independent physician. A fact which resulted in the replacement of secrecy and mystery by communication and discussion, and brought Greek medicine to a high level.

It was in this period Hippocrates stated that diseases cannot be considered as separate entities but that the invalid must be treated in accordance with his condition. The "Hippocratean Corpus" contains a great many pharmaceutical processes, fomentations, poultices, gargles, pessaries, pills, ointments, oils, cerates, collyria, lohochs, troches and inhalations. ("History of Pharmacy", Kremer) It is possible that the many references to the purgatives, sudorifics, emetics and enemas was due to the Hippocratean theory that a requisite in the intestinal treatment of disease was the cleansing of the intestinal tract. A postulate which was still valid a few years back when children were given sulfur and molasses in the spring "to purify the blood."

Although Hippocrates and the "Hippocratean Corpus", were considered authoritative, Western Medicinal Chemistry was influenced more by the teachings of Discarides, Pliny and Galen. Discarides wrote a *Materia Medica* consisting of five volumes, in which were

discussed oils, ointments, root juices, herbs, herbs and roots, cereals and aromatics. He explained the difference between various gums as acacia, gum of cherry, plum, almond and tragacanth as well as the methods of adulteration and means of ascertaining purity.

Pliny, a Roman general, admiral and diplomat, collected and compiled scientific knowledge. Although most of this early knowledge is worthless, nevertheless, here was a serious beginning in recording medicinal facts and prescriptions. Now the popular beliefs in the effects of organic medicines could be studied, applied and verified, or invalidated.

Galen was probably the first physician to point out that observation and experimentation are necessary for knowledge and science. He described over four hundred drugs of vegetable, mineral and animal origin. Three remedies in particular, however, gained worldwide recognition; they are *hiera picra* (holy butter), *terra sigillata* (sealed earth) and *theriaca*. Also, it was he who compounded a formula for cold cream similar to the official *Unguentum Aquae Rosae*. The familiar term "Galenical" is a name which originated with his preparation of composita by mechanical means. Celsius, like Pliny, was a medical encyclopedist but his chief claim to fame is that he translated the Greek medical symbols into Latin. Thus the accumulated knowledge of medicinal chemistry was available to the scientific western world in a common basic language.

In the 13th century the "philosophers' stone" was thought to be the magic substance which would bring about the transformation of base metals into gold and possessed the power to increase longevity and to give health. Although the alchemists failed to find the "philosophers' stone" they did contribute very much to the development of medicinal chemistry. They introduced the use of the spirit lamp, the making of wine, acetic acid, etc.

Arab conquest of the civilized world not only changed the political picture but enriched the medical knowledge of man, in particular medicinal chemistry. Arabian medical treatises describe such drugs as senna, camphor, sandalwood, rhubarb, musk, cassia, tamarind, ambergris, cloves, cubebs and nutmeg. New methods of composing remedies were introduced together with the fashioning of preparations of confections, conserves, juleps and lochochs with sugar or honey.

In 1240 the German Emperor, Frederick II, issued an edict which was the *Magna Charta* of the medicinal chemist. Among other things the Edict separated the pharmaceutical from the medical profession,

supervised pharmaceutical practice, compelled the use of prescribed formulary for the preparation of medicants, limited the number of pharmacies and fixed prices for remedies. This edict, while not adhered to strictly, paved the way to professional status for practitioners of medical chemistry.

From the latter part of the Roman empire most of the manuscripts and comprehensive work on medicinals was kept by the monks and other religious orders. These orders maintained public apothecary shops and were guardians of pharmaceutical knowledge during the frequent upheavals and petty political wars of the time. During the later stage of Arabian influence and church guardianship, medicinal chemistry stagnated. To further hinder development of the young science, the Arabs and the church assumed an attitude of authoritarianism which did not countenance departures from long accepted procedures nor new ideas on physiological action and interaction. Consequently, it was not until the Renaissance that the restrictions imposed by the Arabian and Clerical Scholasticism were overthrown and independent thought reborn.

The causes for sickness, according to the "Hippocratean Corpus", were the different "humors" or, according to Soranus, the different "solids" of the body. Paracelsus, a leading Renaissance figure, believed that sickness is a disturbance of body chemistry. Accordingly, he insisted that the preparation of efficient medicants was the most important part of chemistry. He sought new and more efficient methods for the preparation of tinctures and liquid extracts containing the essential properties of the extracted natural drugs. This is a basic tenet in pharmaceutical chemistry today.

After much controversy and scientific research there evolved an important theory that mixtures of drugs may enhance desired effects or combat the undesirable ones in the cell. This theory of cellular pathology paved the way for a new experimental science, pharmacology, the physiological effect of drugs on animals. This theory formed, also, the basis for the science of chemotherapy and led Ehrlich to find his specific for syphilis, salversan, upon his 606th experiment.

In the later stages of the Renaissance the medicinal chemist was recognized as being in the higher strata of society. In Italy, the apothecary was part of the guild system and had a great deal of political power. In France and Germany the druggist had the social status of a patrician and these two countries set up educational requirements for the profession. England's progress in medicinal

chemistry paralleled that of France and Germany with the exception, perhaps, that professional development was slower and the association of apothecary with quackery remained longer.

The establishment of the American Colonies found the discovery and use of medicinal organic drugs, as usual, in the hands of the men of medico-pharmaceutical practice. In South America the search for aromatic spices and medicinal plants began almost at once but the search was almost a century later in North America. Among a multitude of drugs listed as found new in South America are Angelica, Ginseng, Mandrake, Seneca Snakeroot, Wild Licorice and White Pine. In North America many more were listed in 1925 in the *United States Pharmacopoeia* or in the *National Formulary*. The Maya Indians alone had over 400 uses of various drugs.

A great deal of the credit for the development of early colonial medicinal organic chemistry must be attributed to the religious orders, the Sister Hospitaliers and, particularly, the Jesuit missionaries. These people transplanted the medicinal knowledge of Europe to the colonies and had ample opportunity to use this knowledge in the course of their travels. Father Hannipin, a Jesuit member of La Salle's party in 1680 wrote that in one expedition to the south of the Great Lakes he was taken by the Indians to a salt spring with a surface film of oil. The Indians used the salt as a purgative and the oil as a remedy for rheumatism.

The 17th century saw the isolation of benzoic acid from the pyrolysis of gum benzoin foreshadowing the chemical renaissance of the 18th century; a renaissance which persists even until this day, and whose guiding principle is a careful examination of plant and animal products in their native state with a view of evaluation of their physiological values and their ease of synthesis. Outstanding examples of this type of scientific investigation are, *quinine*, *curare*, *Veratrum Viride*, *penicillum* and *Rauwolfia Serpentina*.

In the eighteenth century the Swedish-German apothecary Scheele conducted a number of experiments which laid the foundation of the chemistry of biological products. He isolated tartaric, citric, malic, gallic, lactic, uric and oxalic acids from their natural products. Also, he isolated glycerol and designated it as the moiety which gave to fats and oils their physical property of sweetness.

The great French chemist Laurent Lavoisier sounded the death knell of the theory of phlogiston in his brilliant series of experiments on oxidation and combustion. It was he together with Priestly who

suggested that oxygen is necessary for the support of animal life. However, it wasn't until the early part of the nineteenth century that Wohler upset the Vital Force Theory which said that organic compounds could be made only by living plants and animals, and synthesized the first organic compound, urea. His work was confirmed, a host of other organic compounds were synthesized and the science of synthetic organic medicinal chemistry was born.

William Henry Perkin in 1856 attempted to synthesize the natural drug quinine, whose empirical formula was known, by the oxidation of crude aniline. He obtained the dye Aniline Purple or mauve. Perkin made a small fortune by manufacturing and selling the dye but, in general, the English nation did little to exploit this discovery. Germany, however, appreciating the importance of Perkin's find, developed the dye industry and the related science, pharmaceuticals. Most dyes are physiologically active and it wasn't long before German scientists with their habitual trait of careful, painstaking, conscientious research held the monopoly on synthetic medicinal chemistry. For example, Prontosil, discovered by Gerhard Domagk, a doctor working for the I. G. Farben Industrie, proved lethal to the dreaded streptococci germs. Previously, there was no known cure for streptococci infection and death was almost certain. Two chemists of the Pasteur Institute in Paris, suspecting that only a part of the large complex dye molecule might be therapeutic, broke the molecule and proved that the sulfanilamide portion possessed all the fantastic infection-fighting properties of the drug.

One of the earliest successes of Paul Ehrlich was with a dye called Trypan Red which was active against the germs of sleeping sickness. It was found, however, that while the dye attacked microbes belonging to the animal kingdom it was helpless against the more common and serious infections caused by bacteria, microbes of the vegetable kingdom. Crystal violet and methyl violet were once used as antiseptics and external bacteriocides but the effect was more psychological than physiological, since the antiseptic value is low and the dye has a fast violet coloration.

Hans Christian Gram discovered stains which helped classify bacteria. Those bacteria which accept color are called Gram-positive and include some of the most deadly germs as streptococci, pneumococci, staphylococci, etc. Bacteria which do not become colored are Gram-negative and have a different type of vulnerability to medicinal compounds.

Not until the end of World War I did the United States enter the pharmaceutical field as a nation. Since then the drug industry has grown to major proportions under the protection of our patent laws and under laws controlling the quality of the drugs on the market.

A statement in the Bible (Revelation xxi, 4) says "Neither shall there be any more pain". This prophecy is progressing toward fulfillment with the application of nitrous oxide, ether, chloroform, ethylene and cyclopropane as anesthetics. Certainly this branch of medicinal chemistry has been not more gratefully received and appreciated by suffering humanity.

The ancient anodynes our forefathers knew; the herbs of drowsiness, hashish, henbane, Galen's lettuce; the narcotics, mandragora, milky juice of poppy and the universal abolisher of pain, alcohol, all were inadequate. The Middle Ages saw the application of pressure on carotid arteries or the jugular vein to produce unconsciousness for surgery; which many times resulted in death, or, if successful, resulted in only short periods of insensibility. Possibly the worst was the compression screw which theoretically deadened the nerves of a limb by pressure before an amputation but produced as much pain as it prevented, and injured all the tissues it compressed.

In the nineteenth century the exhilarating properties of nitrous oxide and the intoxicating properties of ether were recognized in the name, "laughing gas", and the holding of ether parties. Horace Wells, a Boston dentist had nitrous oxide administered to himself and had a tooth extracted. Crawford Long, a physician, removed wens from a patient's neck under the influence of ether; and he, along with Charles Jackson and William Morton, a physician and dentist, respectively, are credited with demonstration of the first practical surgical anesthetic. Chloroform and ethylene were added to the list but the new science of anesthesia encouraged search and synthesis of new and better anesthetics which resulted directly in the discovery of cyclopropane and indirectly in the discovery of the barbituates, novacaine, butacaine, pentothal, etc. Isolation of the alkaloid cocaine from the coca bean made eye surgery possible by completely insensitizing the eye while the patient was still conscious. Even Curare the dreaded poison of the Orinoco Indians of South America is being studied as an anesthetic and antispasmodic. This violent poison paralyzes the ends of the motor nerves of the voluntary muscles leaving the victim helpless but with intelligence not affected so that he dies slowly, a victim of a horrible mental torture as the organs succumb one by one, while

the mind is clear to the end. It is entombed alive within its own cadaver. Curarine, the alkaloid or active principal of curare was isolated in the early nineteenth century and is known to relax the muscles while not affecting the circulation. Since muscular rigidity has always been a surgical obstacle, chemical modification of the drug is being investigated for safe surgical use.

Alexander Fleming's discovery and Howard H. Florey's rediscovery of the bread mold *penicillium notatum* was next to sulfanilamide in the listing of wonder drugs. The chemical synthesized by this mold killed streptococci, staphylococci and pneumococci; the sulfas did not affect the last two classes of microorganisms. Rene Dubas of the Rockefeller Institute for Medical Research discovered a bacterium, *Bacillus brevis*, a rod-like organism which attaches itself to a spherical staphylococcus germ and dissolves its energy into nothingness. Dubas isolated the chemical and called it gramicidin because it was deadly to Gram-positive bacteria. Another active principle tyrocidin was isolated and this mixed with Gramicidin forms the very valuable antibiotic Tyrothricin.

Selman Waksman of Rutgers University isolated the soil bacteria, *Streptomyces griseus*. Thus he discovered streptomycin, a chemical that extended the effective range of antibiotics to include Gram-negative bacteria which except for the gonococcus and the meningococcus, penicillin in the usual concentration, left untouched. Streptomycin killed many kinds of germs but its peculiar specialty was tuberculosis, for which a specific had been sought since the dawn of civilization. Valuable broad spectrum antibiotics as chloromycetin or ampicol, aureomycin and terramycin have been isolated from samples of earth from different parts of the world and the search still goes on relentlessly.

Drs. Philip Hench and Edward Kendall of the Mayo Clinic and Foundation working with cortisone from the adrenal cortex and ACTH from the pituitary found these compounds were very effective against rheumatoid arthritis, rheumatic fever and particularly severe attacks of asthma. These wonder hormones show no discrimination about the different causes of disease but act as if affecting something which is fundamental to all disease.

A great many medicinal organic compounds are being synthesized and tested for treatment of cancer but with little or no success. Among the antagonists or competitive inhibitors of cancer is

the technique of administering extra doses of hormones, male for female patients and female for male patients, which arrest and, in some cases, cure cancers of the breast and prostate, respectively.

In acute leukemia, often called cancer of the blood, Folic acid antagonists arrest the disease for a time. In World War I we used a visicant called "Mustard Gas" and fear of this gas in World War II caused the synthesis of many relatives called "Nitrogen Mustards". These compounds, which are cell poisons, are used for control or necrosis of the rapidly proliferating cancerous cells. Drugs containing radioactive atoms as phosphorus or iodine are used for leukemia and cancer of the thyroid. Vitamin B₁₂, Dr. William Castle's extrinsic factor, is now being used extensively for pernicious anemia. The intrinsic factor is still being sought in the stomach.

In the battle against viruses, the chemical compounds which have living and non-living properties and are small enough to pass through the finest filters, we have the anti-influenza vaccine. Gamma Globulin, the protein part of the blood whose molecules may be changed into antibodies by contact with some types of disease, had been given for poliomyelitis. Now, Dr. Jonas Salk of the University of Pittsburgh has introduced a vaccine for poliomyelitis that is very effective in immunizing people against this disease which reaches epidemic proportions every summer.

Avitaminosis or lack of vitamins has been tied up with alcoholism and certain types of insanity. Dr. Roger Williams of the University of Texas found that administration of the B vitamins cured many alcoholics and a form of insanity that occurs in victims of the deficiency disease, pellagra, could be cured by niacin. A drug called antabuse or TTD has been given to chronic alcoholics with the result that they are unable to tolerate beverages containing alcohol.

Blood clots formed after surgery or occurring in middle-aged people leading a sedentary life, have been a problem for many years. When the clot lodges in the heart or blood vessels of the brain stopping the flow of blood, death results. The discovery of the wonder drugs, Dicoumarol from spoiled clover and Heparin, from mammalian tissue, has circumvented coronary and cerebral thrombosis by liquifying the clot or clots in the circulatory system.

Among the recent drugs developed for treatment of toxic goiter is thiouracil, but it has the serious side affect of destroying certain protective white blood cells, leaving the patient open to the most trivial of infections. Accordingly, newer anti-thyroid drugs as

propylthiouracil, methylthiouracil and tapazole are used with equal effect and little toxicity.

Streptomycin was the first miracle drug found effective against tuberculosis but it soon became apparent that prolonged administration, as was necessary in some cases, causes the antibiotic to become ineffective. The bacillus had built up a resistance. Then came the announcement of the lethal effect of Isoniazid, but as with other anti-TB drugs, the tubercle bacilli built up an immunity with prolonged use. Now, combination of Streptomycin and Isoniazid attack the bacillus in different ways forming a swift lethal combination without allowing time for the germ to form an immunity.

Abnormal concentrations of histamine, a normal metabolite of the body, was thought to be responsible for allergies and, by some scientists, the cause of the common cold. In the 1940s the anti-histamine drugs such as Antergan and then Benadryl were given wide publicity as cures for colds. The lucrative sale of these drugs resulted in the synthesis of thirty more allied drugs by other pharmaceutical houses for the cure of the common cold. Chemical tests failed to uphold the claims of the manufacturer so the government was forced to prohibit further sale. The anti-histamines, on the other hand, do give relief from nausea and vomiting due to pregnancy. Dramamine is used to prevent nausea, seasickness and car sickness. The anti-histamines have been found, also, effective against allergies such as hay fever, bronchial asthma and skin rashes.

While searching for a better anti-histamine, Chlorpromazine or Thorazine as it is known in the United States, was discovered by the scientists of the Rhone-Poulenc Special Laboratories in France. Hoping to develop a drug which would not make people drowsy they tested chlorpromazine on animals and found it had a very quieting effect. For example, rats trained to expect electric shock when a bell rang, did not jump to safety when given chlorpromazine; although their ability to jump was in no wise impaired. Their conditioned fears were allayed.

Smith, Kline and French sold the drug under the name Thorazine and almost at once the remarkable ability to control hyperactivity whether due to nerves or mental derangement, became apparent. Although the effect on mental patients is quick and miraculous in scope, there are many side effects among which are a type of syndrome resembling Parkinsonism—a stooped posture, rigidity of limbs,

tremors, etc. Consequently, Thorazine must be carefully prescribed for each patient.

Other "tranquilizing drugs" are Reserpine (Serpasil) and Azacyclonal (Frenquel). Reserpine, the active principle of *Rauwolfia serpentina*, a plant which has been known and used as a medicinal chemical in India for centuries, is being used for treating high blood pressure. Formerly, hypertension which is possessed by almost half the population of the United States, was treated almost exclusively by the hexamethonium compounds, in particular, hexamethonium chloride. Now, in addition to Reserpine, extracts of the active principle of *Veratrum viride*, the green hellebore, are used very successfully.

In the treatment of epilepsy, a disease which was formerly regarded with shame and a sense of stigmatized ancestry, we have a number of recently discovered organic medicines. For a *grande mal* attack we administer hydantoin derivatives as Dilantin or Mesantoin; *petit mal* attacks are controlled by Tridione or Paradione and the barbiturates.

In early times the field of antiseptics consisted of cauterizing or plunging a glowing hot iron into a wound or amputation stump, pouring boiling oil in gunshot wounds and applying greasy poultices or compositions of animal excrement on cuts or sores. The action of Volcanic ashes against enteric infections and disturbances was known but not understood by primitive man. The Yucatan Indians of New Mexico applied volcanic ash to cuts and wounds. Modern antiseptic treatment begins with the surgeon, Joseph Lister, who used carbolic acid solution as a hand wash and reduced the rate of post surgery mortality from peritonitis. Although the phenol or carbolic acid was excellent for killing bacteria it was very corrosive to the skin so that substituted phenols were synthesized and compared with phenol itself as a bactericide; thus giving rise to the "Phenol coefficient", a term for rating the antiseptic value of new compounds. Dakin introduced chloramine-T and dichloramine-T during World War I as a sterilizing agent for wounds. This proved to be the first important antiseptic on the battlefield and was responsible for sharply reducing the death rate of soldiers from gangrenous wounds. A close relative, Halazone was used in World War II as a powerful antiseptic and germicide for small scale sterilization of water. Methaphen and merthiolate were given wide publicity, at first, as being miraculous antiseptics but they soon were proven inferior to the old standby, tincture

of iodine. The aromatic quaternary ammonium salts such as benzalkonium chloride or "Zephiran chloride" have proved to be useful as non-irritating surface antiseptics and sterilizing agents for surgical instruments and rubber goods. In World War II sulfanilamide powder sprinkled on fresh wounds proved invaluable as a germicide for the medical corps and is used in a great many preparations today for the same purpose.

The field of medicinal chemistry has been closely allied with the physician-surgeon and the study of medicine in general. It has emerged from the shadows of mystery in the hands of the soothsayers, priest-medicinemen, sorcerers, quacks, alchemists and seers, into the light under the guidance of the apothecaries, herb doctors, medieval and Renaissance physicians. Beginning with the field of chemotherapy under Ehrlich, medicinal chemistry has become a recognized and revered science; it has assumed a position of paramount importance in the battle against disease and body disfunction. In a century, perhaps, there will be a medicinal organic compound to successfully treat every disease and abnormality of function in the body.

Like the good Samaritan of biblical times, who anointed with soothing oil and bandaged the wounds of the robbed and assaulted merchant, the science of medicinal chemistry continues to investigate old compounds, synthesize new ones and test both on animals for curative value. Thus the never ending fight continues against human disease and physical frailties so as to encourage the weary, succor the sick and aid the lame; until someday the words *pain* and *suffer* are erased permanently from mankind's book of experience.

THE PREPARATION OF CALCIUM GLUCONATE SOLUTION FOR PARENTERAL ADMINISTRATION

By Eduardo Bechara T. ** and C. Lee Huyck *

THE object of this study was to find the substance which stabilize 10% W/V solutions of calcium gluconate.

In the interest of safety, attempts have been made to increase the stability of this product by both chemical and physical methods. From the physical standpoint (1), calcium gluconate ampuls containing no preservative should be heated two or three times within 72 hour intervals. This operation should be repeated every one or two months. From this, it seems the temperature at which the ampuls are filled and sealed may be significant. Also, solutions of calcium gluconate containing no stabilizer are normally filled while hot in order to avoid crystallization in the filling apparatus.

Heat is less important in the case of solutions containing a stabilizer since the crystallization interval is prolonged. It may be that filling at low pressure would be advantageous, for there must presumably be a condition of negative pressure within the ampuls when these have been filled hot. One theory (2) of decomposition is that a partial vacuum will result in evaporation of the solution at the glass-air interface of the ampul with the formation of crystal nuclei. Accordingly, it might be worth while to investigate: (a) Whether stability would be increased by filling and sealing the solution at a temperature below that of normal storage so that a positive pressure would exist within the ampuls; (b) Whether inverting the ampuls stored upright for some time promotes crystallization.

It has been observed that the addition of calcium d-saccharate lowers the vapor pressure of a calcium gluconate solution. Since the gluconate and saccharate crystallize separately from a solution of the two substances, stabilization is not brought about by the formation of a new chemical compound.

A patent (1) suggests the addition of small quantities of sodium chloride, nucleinates, citrates, glycerophosphates, cacodylates, benzo-

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ates, strychnine salts, codeine salts, glycerin, glucose, gelatin, hexamethylenetetramine, etc., to encourage stability.

The addition of 1% boric acid to 10% calcium gluconate (3) increases the solubility of calcium gluconate in water, due to the formation of an ester between the hydroxyl radicals of calcium gluconate and the boric acid. Since this solution gives an acid reaction of pH 4.2, neutralization by the addition of sufficient quantities of sodium carbonate or sodium hydroxide is indicated (4). However, the toxicity of boric acid (5) in concentrations up to 1% especially when administered intravenously, makes this method questionable for use in this type of pharmaceutical preparation.

Experimental

Aqueous solutions containing approximately 10% calcium salts composed mainly of the gluconate were prepared aseptically for stability studies. The formulas of the solutions are recorded in Table No. I.

TABLE NO. I

FORMULAS OF CALCIUM GLUCONATE SOLUTIONS

	No. I	No. II	No. III	No. IV	No. V	No. VI
Calcium gluconate	20.0 Gm.	19.4 Gm.	20.0 Gm.	20.0 Gm.	20.0 Gm.	19.5 Gm.
Boric acid	0.2 Gm.
Calcium lactate	0.64 Gm.
Sodium benzoate	0.2 Gm.
Pharmagel B	0.2 Gm.
Calcium d-saccharate	0.5 Gm.
Deionized,						
Distilled water	q.s.200	q.s.200	q.s.200	q.s.200	q.s.200	q.s.200
	cc.	cc.	cc.	cc.	cc.	cc.
pH	7.8	7.5	7.6	7.5	7.7	7.8

In order to standardize the working conditions, the six solutions were prepared in a similar manner as follows: Deionized water was freshly distilled. One hundred fifty ml. of this water was placed in an Erlenmeyer flask of 500 ml. capacity. The flask was heated on a water bath at a temperature to 85-90° C. The ingredients were added and the mixture was stirred until solution was effected. Because of the low pH of the solution, sufficient sodium carbonate was added to obtain a pH of about 7.8. Sufficient deionized water was then added to make a total of 200 c.c.

Before filtering, each solution was sterilized in a horizontal autoclave at 15 lbs. pressure for 20 minutes (121° C.). Ten ml. ampuls were washed first with deionized water and boiled for four hours in this water. They were then washed again with a fresh portion of this water and sterilized in an electric oven at a temperature of 120° C. for about six hours. After autoclaving, the six calcium gluconate solutions were heated at a temperature of 40° C. and filtered through a sterile Selas candle filter with water pump attached to safety bottle providing the partial vacuum. The first 15 c.c. of each filtered solution was discarded and the rest filled into ampuls.

The solutions were filled while hot into 10 c.c. ampuls using the Brewer Automatic Filling Machine. Immediately after filling, the ampuls were sealed by a Perfektum semi-automatic sealer using city gas and oxygen at 10 to 12 lbs. per square inch as a source of heat. After standing for twenty-four hours at room temperature the sealed ampuls were sterilized again in the autoclave at 15 lbs. pressure for 20 minutes at a temperature of 121° C. Sterility tests were conducted shortly after manufacture according to the U. S. P. XIV (6) directions.

In order to avoid useless chemical assays of unstable solutions, a preliminary storage screening test was conducted at room temperature, 37.5° C. and 12° C. to find out which solutions showed promise of stability. The results are reported in Table No. II.

TABLE NO. II
OBSERVATION OF CALCIUM GLUCONATE AMPULS AFTER
SIX WEEKS STORAGE

		<i>Precipitation</i>		
		<i>Room</i>	<i>37.5° C.</i>	<i>12° C.</i>
	<i>Sterility</i>	<i>Temp.</i>	<i>Temp.</i>	<i>Temp.</i>
Formula No. I	Sterile	None	None	None
Formula No. II	Sterile	+++	++	++
Formula No. III	Sterile	+++	++	+++
Formula No. IV	Sterile	++++	++++	++++
Formula No. V	Sterile	None	None	None
Formula No. VI	Sterile	None	None	None

++ indicate slight precipitation.

+++ indicate heavy precipitation.

++++ indicate very heavy precipitation.

In order to determine the amount of calcium gluconate present in solution in those ampuls that showed no signs of precipitation, chemical assays were conducted according to the U. S. P. XIV (5). A similar procedure was followed for Formula No. IV, and the results were compared. Results are reported in Table No. III.

TABLE NO. III
PER CENT OF CALCIUM GLUCONATE PRESENT IN AMPULS AFTER
SEVEN WEEKS STORAGE AS COMPARED WITH THEORETICAL
TAKEN AS 100

	<i>Room Temp.</i>	<i>37.5° C. Temp.</i>	<i>12° C. Temp.</i>	<i>Mean Percentage</i>
Formula No. I	99.94	99.97	99.95	99.95
Formula No. IV	36.48	36.40	37.09	36.67
Formula No. V	99.96	99.92	99.93	99.94
Formula No. VI	99.95	99.97	99.96	99.96

Conclusions

1. Six modifications for preparing Calcium gluconate solution for parenteral administration were prepared for stability studies.
2. After seven weeks storage at room temperature, 37.5° C. and 12° C. the formulas containing boric acid, calcium d-saccharate and Pharmagel B as stabilizing agents showed no signs of precipitation. The method of preparation is presented.
3. It is not considered advisable to use boric acid as a stabilizer in the preparation of calcium gluconate solution for injection because of the toxicity of this substance, especially when administered intravenously.
4. Optimal stability of calcium gluconate solutions containing a stabilizer was observed at a pH of 7.8. Adjustment of the pH may be effected by the use of sufficient quantities of sodium hydroxide or sodium carbonate.

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SELECTED ABSTRACTS

The Preparation of Aminophylline Tablets. Whittet, T. D. *Chem. and Druggist* 164:270 (1955). Aminophylline tablets purchased on the market were found to vary in color from white to pale yellow and from odorless to a strong odor of ammonia. No correlation existed between the color and the odor. Bulk aminophylline powder showed similar color and odor.

The author prepared tablets by three methods. Method A involved moist granulation with starch, talc, magnesium stearate and aminophylline. The granules were carefully dried and then compressed into tablets. Method B involved a granulation procedure in which the starch and talc were prepared by moist granulation and then dried. This dry base was then mixed with the aminophylline and a small amount of magnesium stearate and the mixture compressed into tablets. Method C was a slugging procedure in which starch, talc, aminophylline and magnesium stearate were mixed and compressed into slugs. These slugs were broken up and sieved through a 16-mesh sieve, more starch and magnesium stearate were added and the mixture compressed into the finished tablets.

When freshly made, all of the tablets were white or nearly so and were odorless or practically so. After six months and after a year of storage, the tablets made by methods B and C had essentially the same color and odor as when freshly prepared. However, the tablets made by moist compression gradually became brown in color and smelled strongly of ammonia. When samples of the tablets were assayed after six months, those made by method A and B were within the pharmacopoeial requirements for theophylline and ethylenediamine content. Two samples of tablets made by method C had shown a low strength when assayed, one after six months and the other after one year of storage.

The author also found that storage of tablets in screw-capped vials in direct sunlight did not reduce the assayed strength of the tablets. Storage at 37° C. and with a high moisture content in the surrounding atmosphere did not appreciably change the physical characteristics of tablet samples from those reported above, after six months' storage.

BOOK REVIEWS

Vorlesungen über Pharmazeutische Chemie und Arzneimittelsynthese für Studierende und Apotheker. By Prof. Dr. Walter Hückel, Universität Tübingen. Two volumes.

Volume I, Anorganischer Teil. pp. 406. Clothbound; \$11.—
Publisher: Ferdinand Enke, Stuttgart, 1953.

This text represents the lecture material from a four semester course in pharmaceutical chemistry. It is intended to be used primarily by pharmacy students; however, it is the author's intention to make it useful also to the practicing pharmacist since the book provides a commentary to many of the official drugs and preparations. The present edition of the German Pharmacopeia and its commentaries are obsolete; therefore, the subject matter is based to a very great extent on the Pharm. Helv. V, thus making the text valuable for the Swiss pharmacist also.

The first volume deals with the medicinals of inorganic composition only. Special emphasis is placed on pharmacologic action and dosages. The chapter arrangement follows the usual classification. Analytical methods, electronic theories, and the formation of complex compounds are discussed in detail. The chapters on calcium compounds, mineral waters, iodine preparations, phosphorus compounds, and many more are particularly well-written.

Volume II, Organischer Teil. Pp. 717. Clothbound; \$19.00.
1954.

The organic material presented in this volume is grouped according to different aspects:

1. Arrangement according to the classical division of organic chemistry. The chapters on fats, oils, waxes, soaps, etc., carbohydrates and alkaloids follow this usual pattern.
2. Ointment bases, solvents, solubilities are grouped together because of their pharmaceutical application.
3. Most chapters, however, are listed according to their therapeutic effect or pharmacological action. The synthesis of medicinals is discussed in detail. Medical terminology is explained so that the students will become familiar with the terms of the medical profession.

The author deserves credit for writing a text on pharmaceutical chemistry and not simply a textbook on chemistry with pharmaceutical application.

Both the first and the second volume will find their place in the library of the pharmacy student and the practicing pharmacist.

E. EHRENSTEIN

Fisher-Frerichs-Awe; Lehrbuch der Chemie für Pharmazeuten, Lebensmittel—Chemiker, Mediziner und Biologen. By Professor Dr. Walther Awe, Technische Hochschule, Braunschweig. Tenth completely revised and enlarged edition. 2 Volumes. In 8 installments. Third and fourth installments. 160 pp. and 128 pp. respectively. \$4.00. Paperbound. Publisher: F. Enke, Stuttgart.

The third installment is a direct continuation of the discussion of silicon and its compounds (in the second installment) followed by Germanium, the last of the non-metal group. The metallic compounds are grouped according to the established classification. The arrangement is as follows:

Tin and Lead (as metals of the carbon group).

Alkali Metals (basic concepts of analytical chemistry are included).

The Alkaline Earths.

The group of Aluminum: Aluminum, Gallium, Indium, Scandium.

Heavy metals up to Mercury.

The fourth installment continues with Mercury and other heavy metals up to and including Iron. The law of mass action, photography, and colloids are included in these discussions. The chapter on Iron is rather varied. The physiology and the pharmacology of Iron are presented in detail. The smelting of iron ore and the technical production of Iron make for rather interesting reading.

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